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The uptake, distribution and elimination of tin were determined in adult and neonatal (Postnatal Day 5) rat brain following IP administration of triethyltin bromide (TET). Groups of 5 adult CD rats were sacrificed at 10 min, 1 hr, 4 hr, 24 hr, 5 d, or 10 d following acute exposure to 6.0 mg/kg TET; an additional group of adult animals was sacrificed at 24 hr following exposure to either 3.0, 6.0 or 9.0 mg/kg (N=5/dosage). The time course for tin distribution in 5 day-old rat pups was determined by sacrificing pups 10 min, 30 min, 1 hr, 4 hr, 8 hr, 12 hr, 24 hr, 5 d, 10 d, or 22 d following exposure to either 3.0 or 6.0 mg/kg TET (N=4/dosage/time). Tin analyses were performed by flameless atomic absorption spectrophotometry. The $T_{1/2}$ for total tin in the adult rat brain following 6.0 mg/kg TET was determined to be 8.0 days. The maximum concentration in the adult was reached at 24 hrs and corresponded to 4.6, 9.6, and 16.6 ng tin/mg protein for dosages of 3.0, 6.0 and 9.0 respectively. Tin was evenly distributed acorss all brain areas studied. For animals exposed to 6.0 mg/kg TET on postnatal day 5, the $T_{1/2}$ for total tin in the brain was 7.3 days. A maximum concentration of 9.9 ng tin/mg protein was reached at 8 hr post-exposure. The rate of elimination of tin from the brain (as measured by the elimination rate constant $k_{el}$) does not differ significantly between adults and neonates. However due to a dilution effect by the rapid brain growth of the neonate, the concentration of tin in the neonatal brain following TET administration decreases significantly faster than in the adult

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# Tin Distribution in Adult and Neonatal Rat Brain following Exposure to Triethyltin[1]

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Tin Distribution in Adult and Neonatal Rat Brain following Exposure to Triethyltin. COOK, L. L., JACOBS, K. S., AND REITER, L. W. (1984). *Toxicol. Appl. Pharmacol.* 72, 75–81. The uptake, distribution, and elimination of tin were determined in adult and neonatal (Postnatal Day 5) rat brain following ip administration of triethyltin bromide (TET). Groups of five adult CD rats were killed at 10 min, 1 hr, 4 hr, 24 hr, 5 days, or 10 days following acute exposure to 6.0 mg/kg TET; an additional group of adult animals was killed at 24 hr following exposure to either 3.0, 6.0, or 9.0 mg/kg ($N$ = 5/dosage). The time course for tin distribution in 5-day-old rat pups was determined by killing pups 10 min, 30 min, 1 hr, 4 hr, 8 hr, 12 hr, 24 hr, 5 days, 10 days, or 22 days following exposure to either 3.0 or 6.0 mg/kg TET ($N$ = 4/dosage/time). Tin analyses were performed by flameless atomic absorption spectrophotometry. The $t½$ for total tin in the adult rat brain following 6.0 mg/kg TET was determined to be 8.0 days. The maximum concentration in the adult was reached at 24 hr and corresponded to 4.6, 9.6, and 16.6 ng tin/mg protein for dosages of 3.0, 6.0, and 9.0 mg/kg, respectively. Tin was evenly distributed across all brain areas studied. For animals exposed to 6.0 mg/kg TET on Postnatal Day 5, the $t½$ for total tin in the brain was 7.3 days. A maximum concentration of 9.9 ng tin/mg protein was reached at 8 hr postexposure. The rate of elimination of tin from the brain (as measured by the elimination rate constant $k_{el}$) did not differ significantly between adults and neonates. However, due to a dilution effect by the rapid brain growth of the neonate, the concentration of tin in the neonatal brain following TET administration decreased significantly faster than that in the adult.

The toxic effects of triethyltin (TET) on the mature vertebrate central nervous system have been well documented (Watanabe, 1980). Administration of TET to the adult rat results in interstitial edema in the brain and spinal cord white matter which is characterized by vacuolation (spongy degeneration) of the myelin sheath at the interperiod line (Magee *et al.*, 1957). The behavioral toxicity of TET is characterized by impaired motor function resulting in hypoactivity, impaired grip strength, and reduced amplitude of the startle response (Squibb *et al.*, 1980; Reiter *et al.*, 1980). Both the behavioral and pathological effects are reversible upon termination of exposure.

In contrast, neonatal exposure to TET produces a different profile of neurotoxic effects (Reiter *et al.*, 1980; Reiter, 1982). Wender *et al.* (1974) showed that TET exposure in the 6-day-old rat resulted in reduced brain weight and delayed myelinogenesis, but that cerebral edema does not occur. Acute exposure to TET on Postnatal Day 5 was reported to produce

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delays in motor development and impaired startle response, reduced brain weight and hyperactivity which persist into adulthood (Harry and Tilson, 1981; Reiter *et al.*, 1981).

At least two mechanisms may account for these age-related differences in the toxicity of TET. First, during the early postnatal period, the rat brain undergoes a period of rapid growth which Dobbing (1968) termed the "growth spurt." Therefore, differences in toxicity may be due to differences in the functional susceptibility of the nervous system related to these maturational changes. Second, the neonatal rat has been reported to show a higher whole body retention of heavy metals as well as higher levels of accumulation in the brain (Kostial *et al.*, 1978; Jugo, 1977). Therefore, differences in toxicity may be due to differences in the amount of chemical reaching the nervous system.

Previous studies exist describing tin distribution following the administration of TET in the adult (Rose and Aldridge, 1968; Brody and Moore, 1962). The object of the present study was to compare the distribution of tin in the adult and neonatal rat brain to determine whether a difference in either peak levels or persistence of tin could be a contributing factor to the age-related differences in the toxicity of TET.

## METHODS

*Animals.* Animals used in these studies were CD rats obtained from Charles River Breeding Labs, Wilmington, Mass. Neonatal exposure utilized offspring of time-pregnant females obtained 2 days after mating; adult exposure utilized male rats obtained at 60 days of age. Animals were housed in cages measuring 45 × 24 × 20 cm in an animal facility controlled for temperature (22 ± 2°C) and humidity (50 ± 10%) and maintained on a 12:12-hr light:dark cycle beginning at 0600 hr. Adult males were housed 3/cage whereas dams (with litters) were housed individually. Food (Purina Lab Chow) and water were available *ad libitum* throughout the experiment.

*Adult dosing.* To determine the time course for tissue distribution of tin, rats received a single ip injection of either vehicle (sterile isotonic saline) or 6.0 mg/kg TET-Br (Alpha Products, Danvers, Mass.); the injection volume was 1 ml/kg body weight. A single group of vehicle controls ($N = 5$) was killed 4 hr after injection. Groups receiving 6.0 mg/kg were killed at 10 min, 1 hr, 4 hr, 24 hr, 5 days, or 10 days after exposure ($N = 5$/group). Approximately 5 min prior to death, each animal was injected with 1.3 ml Chloropent (Fort Dodge Laboratories, Fort Dodge, Iowa). The thoracic cavity was opened and a perfusion tube was placed in the aorta by passing it through the heart. After perfusion with isotonic saline, the liver, kidneys, and brain were removed, sealed in scintillation vials, and stored at −60°C until the tin assays were performed.

To study total tin levels in whole brain as a function of dosage, rats were exposed to either 3.0, 6.0, or 9.0 mg/kg ($N = 5$/dosage) and killed 24 hr later. This interval corresponds to the time of peak tin concentrations in the brain.

Tin distribution in various brain areas was also determined 24 hr after administration of 9.0 mg/kg ($N = 5$). The following brain regions were analyzed by the dissection procedure of Glowinski and Iversen (1966): hypothalamus, striatum, hippocampus, cerebellum, medulla-pons, forebrain (minus striatum), and hindbrain (remaining brain). Death, perfusion, and storage of tissue were as described above.

*Neonatal dosing.* At parturition (Day 0), pups were randomized and each dam was assigned 4 male and 4 female pups. On Postnatal Day 5, pups received a single ip injection of either 0, 3.0, or 6.0 mg/kg TET-Br in a volume of 10 ml/kg body weight. A single group of vehicle controls ($N = 8$) was killed 5 days after exposure. Pups receiving either 3.0 or 6.0 mg/kg TET were killed at 10 min, 30 min, 1 hr, 4 hr, 8 hr, 12 hr, 24 hr, 5 days, 10 days, or 22 days ($N = 4$/dosage/time). After death by decapitation, brains were quickly removed and stored in polycarbonate vials at −60°C.

*Tin analyses and calculations.* Tissues were thawed and homogenized in 4 vol (liver in 2 vol) of 2% nitric acid (ACS grade, Fisher Scientific, Springfield, N.J.) in glass homogenizers with a Teflon/stainless-steel pestle. These samples were acid digested by a modification of the procedure described by Mushak *et al.* (1982). Aliquots of the homogenate were combined with an equal volume of concentrated nitric acid (ACS grade, Fisher Scientific) and digested overnight at room temperature. The digested samples were well mixed and aliquots were transferred to polystyrene sample vials (Lancer) and placed in the autosampler. Tin quantification was based on the method of additions by standard curves which were prepared by spiking replicate aliquots of homogenate with known amounts of TET-Br. A typical coefficient of variation within triplicate atomic absorbance analyses of samples was 3.6%. Standard solutions of TET-Br were compared to a certified tin atomic absorbance reference standard and found to be accurate in molarity of tin. Protein determinations were performed on the homogenates of all

tissue by the method of Lowry *et al.* (1951), and tin concentration was expressed as ng tin/mg protein in the homogenized tissue. The percentage of the total TET dose found in the brain was also calculated. Tin levels in different brain areas were compared by analysis of variance at the 0.05 level of significance (SAS, 1982).

Linear regression analyses were used to calculate the elimination rate constant ($k_{el}$) and half-life ($t½$) of tin in both adults and neonates. These analyses were performed for both log (tin concentration) and log (total tin) versus time, with values from the descending portion of the elimination curves. The $k_{el}$ was calculated as the slope of the regression line × 2.303, and half-life defined as $0.693/k_{el}$ (Klaassen, 1980).

*Apparatus.* A Perkin–Elmer Model 603 atomic absorption spectrophotometer equipped with a Perkin–Elmer Model HGA-2100 graphite furnace and Model AS-1 auto sampling system was used. A Perkin–Elmer tin electrodeless discharge lamp was used for increased stability and sensitivity at low tin concentrations. Deuterium background correction was also employed. Graphite furnace power supply parameters were set as follows: dry: 90°C, 30-sec ramp, and 30-sec hold; char: 1000°C, 30-sec ramp, and 60-sec hold; and atomize: 2700°C, 5-sec hold. The analytical wavelength used was 224.6 nm, the slit width was 1 mm, and the band pass was 0.7 nm. Untreated graphite tubes were used, and the flow gas was nitrogen, with interrupt mode used during atomization.

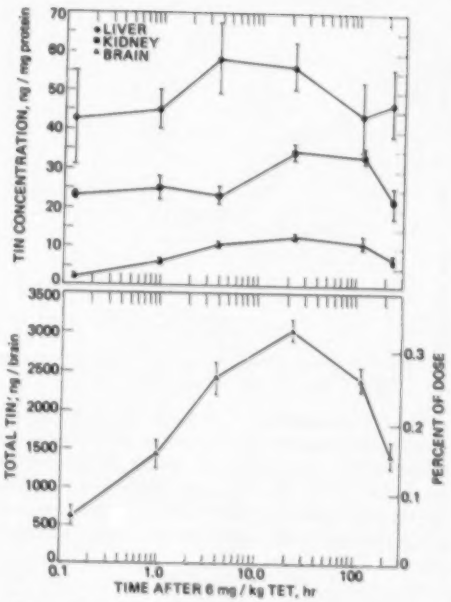


FIG. 1. (Top) Concentration of tin in liver, kidney, and brain in adult rats following exposure to 6.0 mg/kg TET, ip. (Bottom) Total tin and percentage of dose in adult brains after 6.0 mg/kg TET, ip. Percentage of dose: the mean value for total tin in whole brains of the 24-hr exposure group is 0.33% of their average dose. Each data point is the mean ± SE of 5 animals.

## RESULTS

Tin was not detectable in any tissue studied from vehicle control animals, which were included in all studies. The limit of detection was approximately 10 ng tin/ml of brain homogenate which was equivalent to 0.3 ng tin/mg of brain tissue. Data are presented for TET-exposed animals only.

*Adult exposure.* The time courses for tin distribution in brain, liver, and kidneys of adult rats exposed to 6.0 mg/kg TET are presented in Fig. 1. The greatest accumulation of tin was measured in the liver which showed a peak concentration of 58.2 ng/mg protein at 4 hr postinjection. For kidneys and brain, tin levels peaked at 24 hr postinjection and were 34.5 and 12.6 ng/mg protein, respectively. For brain, this peak concentration corresponds to 0.33% of the total dose (see bottom of Fig. 1). There was a dose-related increase in the concentration of tin in whole brain measured 24 hr after exposure. Following 3.0, 6.0, and 9.0 mg/kg TET, the resulting whole brain tin concentrations (±SE) were 4.6 (±0.8), 9.6 (±0.8), and 16.6 (±1.1) ng tin/mg protein, respectively. However, as shown in Fig. 2, there was no significant differential distribution of tin in the brain areas examined [ANOVA, $F(6,28) = 1.83$, $p \leq 0.13$].

*Neonatal exposure.* Neonatal exposure to either 3.0 or 6.0 mg/kg TET resulted in detectable whole brain levels of tin within 10 min after exposure (Fig. 3). Following 6.0 mg/kg TET, a maximum concentration of 9.9 ng tin/mg protein occurred 8 hr after exposure; the peak amount of total tin corresponded to 1.5% of the total dose (bottom of Fig. 3). The brain concentration of tin following 3.0 mg/kg TET was approximately 5 ng/mg protein

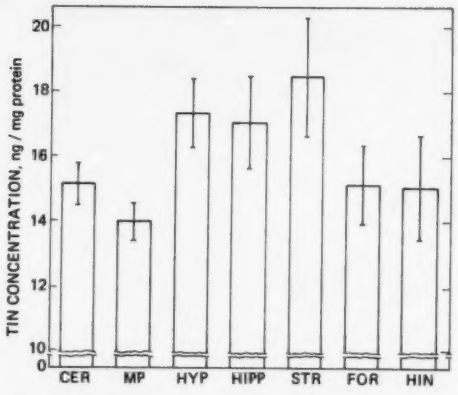


FIG. 2. Concentration of tin in various brain regions of adult rats measured 24 hr following an ip injection of 9.0 mg/kg TET. Each value is the mean ± SE of 5 animals. Cerebellum (CER); medulla-pons (MP); hypothalamus (HYP); hippocampus (HIP); striatum (STR); forebrain minus striatum (FOR); and hindbrain minus hypothalamus and hippocampus (HIN).

between 1 hr and 5 days and no clear peak was seen.

*Elimination rate constants and half-lives.* $k_{el}$ and $t½$ values are presented in Table 1. When calculated on the basis of total tin, there was no significant difference in the rate of elimination of tin from the brain between neonates and adults. However, when the rate of change of tin concentration was calculated, tin concentration decreased nearly twice as fast in the neonate as in the adult brain (Fig. 4).

## DISCUSSION

Rose and Aldridge (1968) studied the distribution of tin in rats following iv administration of triethyltin chloride labeled with $^{113}Sn$. Their data indicate that peak levels of tin in the brain were reached between 4 and 24 hr. Our data agree with this finding. Tin concentration in the liver peaked at an earlier time (4 hr) than in the brain or kidney, as might be expected following ip administration. The dose-related increase in tin concentration indicates that, over the dosage range studied, entry of tin into the brain is a nonsaturable phenomenon. The finding that tin is distributed evenly across brain areas is in agreement with Rose and Aldridge (1968).

Although peak concentrations of tin are comparable in the adult and neonate, a greater percentage of the administered dose is observed in the neonate brain than in the adult brain (1.5% as compared to 0.33%). One factor which may contribute to this difference is the greater relative brain weight of the neonate (4%) vs that for the adult (0.33%). If tin distribution were determined solely on the basis of organ weight, however, the neonatal brain should be receiving 4% of the administered dose rather than only 1.5%. Therefore the neonatal brain accumulates a higher percentage of the administered dose than does the adult brain, but less than would be expected on the basis of brain weight relative to body weight.

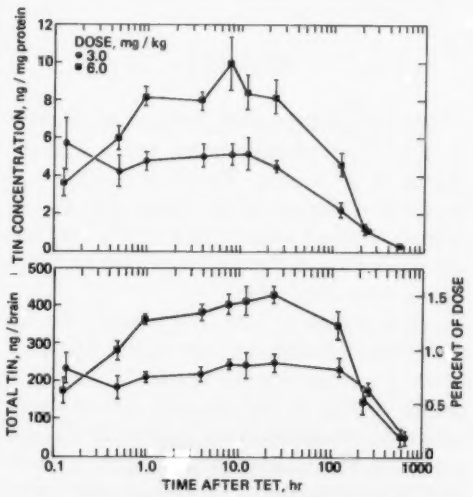


FIG. 3. (Top) Time course for tin concentration in neonatal rat brain following 3.0 and 6.0 mg/kg TET, ip. (Bottom) Total tin and percentage of dose in neonatal brains after 3.0 and 6.0 mg/kg TET, ip. Percentage of dose: the mean value for total tin in whole brains of 24 hr, 6.0-mg/kg exposure group is 1.5% of their average dose. Each data point is the mean ± SE of 4 animals.

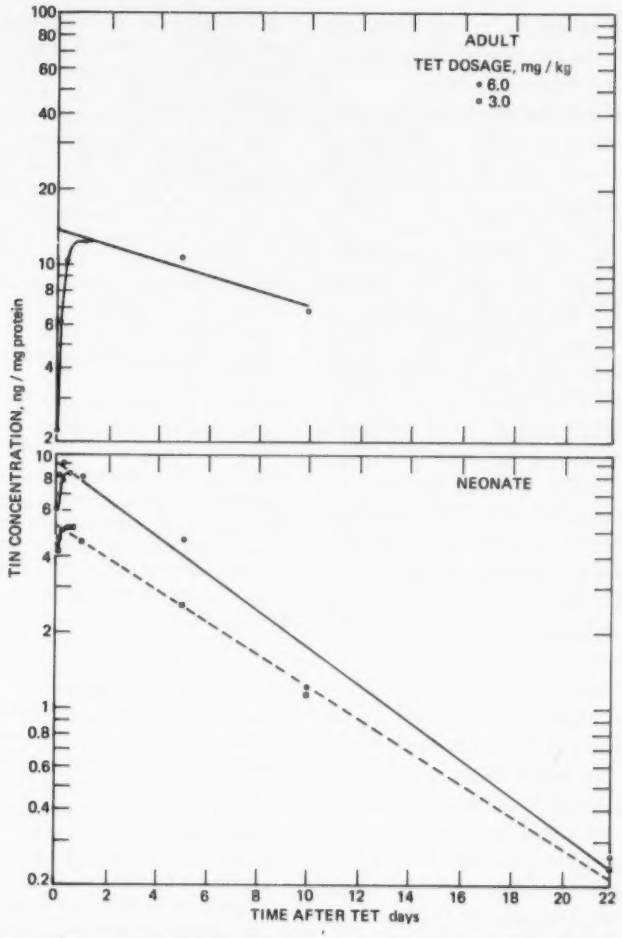


FIG. 4. (Top) Log of tin concentration in adult brain following 6.0 mg/kg TET, ip. (Bottom) Log of tin concentration in neonatal brain following 3.0 and 6.0 mg/kg TET, ip.

TABLE 1

ELIMINATION RATE CONSTANTS AND HALF-LIVES OF TIN BASED ON TOTAL TIN AND TIN CONCENTRATION IN ADULT AND NEONATAL RAT BRAIN

| | Total tin | | Tin concentration | |
|---|---|---|---|---|
| | $k_{el}$ | $t½$ | $k_{el}$ | $t½$ |
| Adult | 0.087 | 8.0 | 0.082 | 8.5 |
| Neonate | 0.094 | 7.3 | 0.16 | 4.3 |

The elimination rate constants and $t½$ values for total tin in the brain differ little between adult and neonates. This finding indicates that the process for clearance of TET from adult and neonatal brains may be similar. This conclusion differs from results reported by Kostial *et al.* (1978) for inorganic metals, which indicate a slower clearance in the neonate than in the adult. The rate of decrease of concentration, however, is much greater in the neonate. This difference is likely the result of a

dilution effect due to increases in protein and other constituents in the rapidly growing rat brain (Agrawal and Himwich, 1970).

These data indicate that following Postnatal Day 5 administration of TET, a significant amount of tin persists in the brain for several days. This time period of exposure encompasses the proliferative period of many cell types, including the maximum proliferation of oligodendroglial cells close to Day 5 (Schonbach *et al.*, 1968) and the beginning of myelinogenesis at Day 7 (Gottleib *et al.*, 1977), as well as many other processes (Davison and Dobbing, 1968). O'Callaghan *et al.* (1983) demonstrated that Postnatal Day 5 administration of TET causes a decrease in myelin basic protein (a marker for total myelin content) and hypothesized that TET interferes with myelinogenesis. Our data are consistent with this hypothesis in demonstrating that following Postnatal Day 5 administration of TET, measurable tin levels persist well into the period of myelinogenesis.

In considering the toxicity of TET, however, it may be more appropriate to look at the concentration of tin (ng tin/mg protein) rather than total tin. As noted earlier, the rapid growth of the neonatal brain has the effect of diluting the tin concentration, and may be as effective in reducing the toxic potential of TET as actual elimination of tin from the brain. This finding would indicate that TET may be producing its toxic effects in a relatively short time following Postnatal Day 5 administration, supporting the findings of Reiter *et al.* (1982) that injection of TET on Postnatal Day 10 or 15 fails to produce the same spectrum of behavioral effects as Postnatal Day 5 administration. Thus it appears that the sensitivity of the neonate to TET is not due to higher levels or prolonged exposure, but rather to the presence of TET during a sensitive critical period in development.

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